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Cause, consequence or coincidence: The relationship between psychiatric disease and metabolic syndrome

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ABSTRACT

It is now well established that severe mental illness (SMI) is associated with a reduced lifespan and increased risk of cardiovascular disease (CVD). Individuals with SMI often have abnormalities of lipid metabolism, glucose homeostasis, an increased prevalence of obesity and hypertension. They also have an increased prevalence of Metabolic Syndrome (MetS). The reasons for this are not entirely clear, but are likely to be multifactorial. Whilst there have been numerous studies investigating the prevalence of MetS in patients with SMI, many have been in small, mixed population samples, that have not been adequately controlled for the background population from which they have been drawn. This is important because of the wide range of prevalence estimates that have been reported, and variations of MetS prevalence with ethnicity. The negative impact of treatment with second-generation antipsychotic (SGA) drugs on the risk of MetS also appears clear in most populations, although the mechanisms accounting for this increased risk are yet to be clarified. Despite this high prevalence of CVD risk factors in patients with SMI, most studies report a poor implementation of screening for CVD risk factors at baseline, and following initiation of treatment with SGAs. Not all patients with SMI are susceptible to the adverse effects of SGAs, but in those that are, switching to an anti-psychotic that is less likely to cause metabolic disturbance, starting statin therapy and a reduction in CVD risk factors through changes in lifestyle may all be important strategies.

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1. Introduction

Severe mental illness (SMI) is associated with a substantially reduced life expectancy.^{1,2} The complexity of defining SMI has been outlined by the Director of the US National Institute of Mental Health,³ and in the United States (US) a practical and pragmatic approach has been used⁴; SMI therefore comprises psychotic and affective disorders that lead to functional impairment that affect major life activities. The increased risk of premature cardiovascular disease (CVD) in individuals with SMI is particularly notable, and this has been attributed, in part, to a high prevalence of metabolic syndrome (MetS). The latter condition, also termed Syndrome X by

Reaven,⁵ is characterised by a clustering of several CVD risk factors that include central obesity, dyslipidaemia, hypertension and impaired glucose tolerance. Reaven has argued that insulin resistance (IR) is the central metabolic defect in MetS. Bjorntorp noted that stress-related cortisol secretion is often enhanced in individuals with central obesity and that this may lead to IR and the other features of MetS.⁶ His team further observed that the hypothalamic-pituitary adrenal (HPA) axis may be stimulated by several socio-economic and psychosocial factors, which include: alcohol, smoking and traits of psychiatric disease.⁷ Therefore, the relationship between major psychiatric conditions such as schizophrenia and bipolar disorder (BD), and risk of MetS and cardiovascular disease (CVD) may be due to:

- 1) SMI being a cause of MetS, due to the direct effects of psychiatric disease, or its treatment,^{8,9} on the metabolic and hormonal milieu,¹⁰ or on patterns of behaviour that increase the risk of the components of MetS;^{11,12}
- 2) SMI being a consequence of the potential impact of the MetS,¹³ and particularly obesity,¹⁴ on mental wellbeing,¹⁵ or

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Abbreviations

AHA	American Heart Association
ATPIII	National Cholesterol Education Programme, Adult Treatment Panel-III
ATPIIIa	adapted ATP-III
AUD	Alcohol use disorder
BD	Bipolar disorder
BMI	Body mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
CVR	Cardiovascular risk
DM	Diabetes mellitus
FES	First episode schizophrenia
HDL-C	High-density lipoprotein-cholesterol
HRLQ	Health related quality of life
HOMA	Homeostasis model assessment
HPA	Hypopituitary-pituitary-adrenal
ICD	International Classification of Diseases
IDF-AHA/NHLBI	International Diabetes Federation-American Heart Association/National Heart Lung and Blood Institute
IDF	International Federation of Diabetes
IFG	Impaired fasting glucose

IGT	Impaired glucose tolerance
IR	Insulin-resistance
IS	Insulin-sensitivity
JIS	Joint Interim Statement
LDL-C	Low-density lipoprotein-cholesterol
MDD	Major depressive disorder
MI	Myocardial infarction
MetS	Metabolic Syndrome
MTHFR	methylenetetrahydrofolate reductase
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PCOS	Polycystic ovary syndrome
PHQ-9	Patient Health Questionnaire-9
PPARs	Peroxisome Proliferator-Activated Receptors
PTSD	Post-traumatic stress disorder
QUICKI	Quantitative insulin check index
ROC	Receiver operating characteristic
SGAs	Second-generation antipsychotics
SMI	Severe mental illness
SSRI	Selective serotonin uptake inhibitor
TG	Triglycerides
TPH2	Tryptophan hydroxylase 2
UA	Uric acid
US	United States
VPA	Valproic acid
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

3) Individuals being affected by SMI and MetS co-incidentally because of shared common risk factors, that may include a genetic predisposition,¹⁶ sleep disorders,¹⁷ or stress,¹⁸ that predispose to both psychiatric disease and metabolic abnormalities.¹⁹

These putative mechanisms are not mutually exclusive; the relationships may be bidirectional and self-reinforcing (see Fig. 1). For example, whilst depression can predispose to CVD; CVD may also lead to depression, and several socio-economic and behavioural

correlates of both conditions may further influence this relationship.²⁰

In this review, these possible complex relationships are explored further, together with the reported prevalence of MetS in different SMIs (schizophrenia, schizoaffective disorder, bipolar disorders, depression, stress related disorders and substance dependency) and different global population samples. The interpretation of prevalence estimates of MetS in populations with psychiatric disease is complicated. This is particularly the case with respect to historical and global data, because of the different criteria

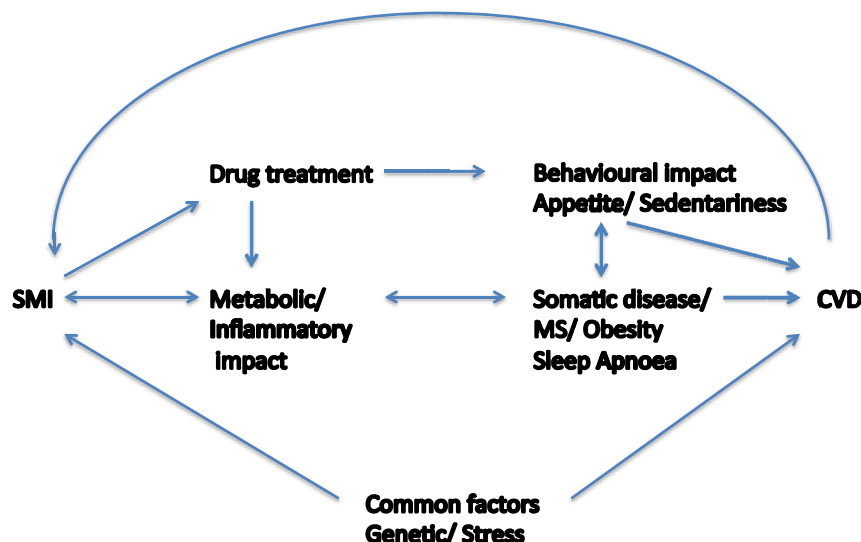


Fig. 1. Interactions between factors related to severe mental illness (SMI) and cardiovascular disease (CVD) risk factors, including Metabolic Syndrome (MS).

that have been used to define MetS,^{21–23} the changes in these definitions over time, and the differences in these definitions between ethnic groups.²⁴ Furthermore, the high frequency of undetected co-morbidities, such as chronic liver disease, may confound the interpretation of metabolic profiles in patients with psychiatric disease.²⁵ The potential impact of drug treatment for SMIs on the risk of MetS is also explored, together with some of the potential mechanisms that may account for this increased risk, using evidence from different types of study. The review concludes with a brief discussion of the possible approaches to the management of CVD risk in patients with SMI, using drugs and lifestyle interventions.

2. Prevalence of metabolic syndrome and its components in mixed populations of psychiatric conditions [Table 1]

Some of the early papers on the relationship between psychiatric disease and MetS are reviewed below for completeness. However, they often did not make a distinction between the categories of SMIs, and more recent studies have looked more carefully at this, and do indeed report a significant differential association.²⁶

In a large, nationally representative group of 8028 Finns (>30 years old), the prevalence of MetS, using ATP III criteria, differed between categories of SMI; prevalence estimates were 36.2%, 41.4%, and 25.0% among subjects with schizophrenia, other non-affective psychosis, and affective psychosis, respectively, and 30.1% for subjects without psychotic disorders. The individuals with schizophrenia had significantly lower serum high-density lipoprotein cholesterol (HDL-C) and higher triglyceride and glucose levels, and larger waist circumference, than the other study groups. Among subjects with other non-affective psychotic disorders, only the difference in waist circumference was statistically significant ($p < 0.05$). The prevalence of MetS was significantly higher among users of high-potency antipsychotics (52.1%), but not for those on low-potency (39.0%) and atypical (23.4%) antipsychotic medication.²⁷ MetS was also reported to be more common amongst patients receiving poly-pharmacy with multiple antipsychotics and

mood stabilisers.⁸ In this same population, individuals with schizophrenia also had a metabolically unfavourable body composition, comprising abdominal obesity, high fat percentage and low muscle mass.²⁸

Data from a mixed population of in-patients with SMI from Western Australia showed that the percentage of obese patients (30.3%) was significantly higher than for the general population (21.4%), with women showing a greater propensity toward obesity than men. In this sample, individuals with personality disorders had a mean BMI in the obese range (30.07 kg/m²), and at a 9 month follow-up, there were further increases in weight.²⁹

Prior to the extensive use of antipsychotics, MetS was estimated to be approximately two to three times more prevalent in SMIs compared to the general population. However, the major psychotropic drugs used to treat SMIs today may further exacerbate this increased risk of MetS.³⁰ In an Italian study, MetS was present in 35.2% in-patients with SMI, when defined according to ATP III modified criteria. The sample contained 29.6% of patients with schizophrenia spectrum and other psychotic disorders, 37.6% of those with bipolar and related disorders, 22.4% in depressive and 10.4% with personality disorders. Regression analysis, showed that the use of atypical antipsychotic treatment was an important determinant of MetS.³¹

There have been few studies that have compared prevalence rates of metabolic abnormalities in patients with different psychiatric disorders being treated with antipsychotic drugs. In patients (>40 years old) requiring antipsychotic treatment, the overall prevalence rates of MetS were very high: 72% in patients with Post-Traumatic Stress Disorder (PTSD), 60% in those with schizophrenia, 58% in those with mood disorder, and 56% in those with dementia. The overall frequency of MetS and its components in patients with PTSD taking antipsychotics was similar to that of patients with schizophrenia.³² The 10-year risk of CHD, calculated using the Framingham risk score, was also greatest in patients with schizophrenia and PTSD in this population sample.³³

A cross-sectional study investigated the prevalence of MetS among psychiatric inpatients in Kashmir, Northern India. The

Table 1
Reported prevalence of metabolic syndrome in mixed groups of patients with serious mental illness.

Reference	Suvisaari et al. ²⁷	Jin et al. ³²	Gossell-Williams et al. ⁴⁰	Ko et al. ⁴³	Solia et al. ³¹	Hussain et al. ³⁵	Alosaimi et al. ³⁶	Saloojee et al. ⁴²
Date	2007	2009	2012	2013	2015	2017	2017	2017
Country	Finland	USA	Jamaica	South Korea	Italy	India	Saudi Arabia	South Africa
Setting	Nationally Representative	OP on anti-psychotics	IP	IP and OP	IP	IP	IP	IP on anti-psychotics
N	8028	203	38	1103	125	213	992	232
Age group	>30	>40						
Design	CS	CS	CS	CS		CS		CS
MS definition	ATPIII	AHA	IDF/ AHA	ATPIIIa IDF	ATPIIIa	ATPIII		JIS
%MS								
Control	30.1							
SMI			28.9	ATP 43.9 IDF 40.1	35.2	34.7	41.2	F37.7 M10.3
Schizophrenia	36.2	60						
NA Psychosis	41.2							
Aff Psychosis	25.0					31.0		
Depression						43.3		
BD						37.9		
PTSD		72						
Dementia		56						
Anti-psych								
High potency	52.1							
Low Potency	39.0							
Atypical	23.4					63.6		

Aff = Affective; AHA = American Heart Association; ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III; ATPIIIa = adapted ATP-III; Anti-Psych = Antipsychotics; BD = Bipolar Disorder; CS = Cross-sectional; IDF = International Diabetes Federation; IP = In patient; JIS = Joint Interim Statement; MS = Metabolic syndrome; NA = non-affective; OP = Out-patient; PTSD = post-traumatic stress disorder; SMI = severe mental illness.

modified ATP III criteria were used to define MetS in 213 patients with a psychiatric diagnosis based on the International Classification of Diseases, Tenth Revision (ICD 10) Classification of Mental and Behavioural Disorders criteria.³⁴ The overall prevalence of MetS was approximately 34.7%. It was higher in women (43.3%) than men (28.5%) ($p < 0.05$) and increased with age. The highest prevalence was among patients with unipolar depression (45.0%), and was lower in patients with bipolar disorder (BD) (37.9%) and psychotic disorders (31.0%). The prevalence of MetS was significantly higher (63.6%) among patients taking SGAs ($p < 0.05$).³⁵

In a cross-sectional study conducted among adult patients with psychiatric disorders at major hospitals in Saudi Arabia, the prevalence rate of MetS among the 992 study participants was 41.2%. High fasted serum triglycerides were present in 32.8%, a high waist circumference in 42.2%, high blood pressure in 42.5%, high fasting blood glucose in 47.8%, and a low serum HDL cholesterol was found in 52.5% of patients. Patients with MetS were more likely to be older, illiterate, divorced or widowed, have a higher number of children, older age of onset of psychiatric illness, longer duration of psychiatric disease, no previous psychiatric hospitalization, and have a history of diabetes and hypertension. After adjusting for significant demographic and clinical characteristics, none of the psychiatric diagnoses and treatments was independently associated with MetS, except for the use of the anti-depressants, mirtazapine and venlafaxine.³⁶

An Ethiopian cross-sectional study of 1924 adults, assessed socio-demographic data, behavioural characteristics and major depressive disorder (MDD) symptoms using the Patient Health Questionnaire-9 (PHQ-9) depression scale.³⁷ There were a total of 154 participants with MDD. Among women, MDD was associated with more than 4-fold increased risk of diabetes mellitus (OR = 4.14; 95% CI: 1.0316.62). Among men the association was not significant (OR = 1.12; 95% CI: 0.63–1.99); MDD was not associated with MetS among women, or men in this population.³⁸

A Swedish study of 731 patients with psychosis reported that they had a significantly higher waist circumference compared with controls drawn from the same area, after controlling for fasting insulin, differences in gender, blood pressure, fasting glucose, family history of diabetes, age and tobacco use. An increased fasting blood glucose was also more common in the psychotic patients (OR = 2.41; 95% CI 1.84–3.14) after controlling for confounding factors.³⁹ In a small sample ($n = 38$) of Jamaican adult psychiatric inpatients, the prevalence of MetS, using IDF criteria, was 28.9%.⁴⁰

It has been reported previously that the prevalence of MetS is higher among black women compared to black men living in South Africa.⁴¹ This has been more recently investigated among black South African participants with SMI (male 155 and female 77) taking antipsychotic medication, and 232 matched controls without SMI (male 156 and female 76). The Joint Interim Statement (JIS) criteria were used to define MetS. The prevalence of MetS was more than three times higher in women with SMI compared to men with SMI (37.7% vs. 10.3%, $p < 0.001$). There was no significant difference in the prevalence of MetS in men or women between the groups with and without SMI. In multivariate logistic regression analysis, female gender (OR = 7.66), advancing age (OR = 1.08) and longer duration of illness (OR = 1.15) were significant risk factors for MetS in individuals with SMI. Hence, in black South Africans with SMI on antipsychotic medication, there was a substantially higher prevalence and risk for MetS in women compared to men.⁴²

Data were collected from the medical records of 1103 inpatients and outpatients treated for schizophrenia at Seoul National Hospital in Seoul, Korea. MetS prevalence data were compared by gender, age, MetS components, treatment for these components, and types of antipsychotics and individual drugs used. The prevalence of MetS in all subjects was 43.9% and 40.1% according to

adapted ATP-III (ATP-IIIa) and IDF criteria, respectively. No significant differences were found in prevalence according to ATP-IIIa criteria between men (42.6%) and woman (45.9%). A trend toward a higher prevalence with age was observed for both sexes up to 50 years, followed by a continued increase for women but a decrease for men. Use of a combination of atypical antipsychotics was associated with the highest MetS prevalence and use of aripiprazole with the lowest.⁴³

In these studies of populations with mixed SMI, a higher prevalence of MetS above the background has been reported in population samples from Europe, Asia and Africa. This appears to be affected by gender, ethnicity and category of SMI, together with the drug therapy used (SGAs, atypical antipsychotics and polypharmacy).

3. Prevalence of metabolic syndrome and associated features in patients with schizophrenia [Table 2]

Schizophrenia is a severe mental disorder that affects more than 20 million individuals globally.⁴⁴ It is associated with “distortions in thinking, perception, emotions, language, sense of self and behaviour.” People with schizophrenia can experience both hyper- and hypo-function of the HPA axis. It is likely that this contributes to the pattern of poor physical health and premature mortality that they suffer, in particular the high rates of cardiovascular and metabolic disturbance.⁴⁵ It has been estimated that schizophrenia is associated with a 20 year reduction in lifespan, with an increased prevalence of type 2 diabetes mellitus and CVD contributing the most to the increased mortality.⁴⁶ Unrecognised, or silent myocardial infarction (MI) appears to occur frequently among patients with schizophrenia and this may also contribute to the increased mortality in this patient group.⁴⁷

Baseline data from the Oslo TOP Study (including individuals with BD [$N = 110$] and schizophrenia [$N = 163$]) were compared to reference data, obtained from the Oslo Health Study in 2001 (comprising 18,770 individuals who were drawn from the same locality). There was no significant difference between the two diagnostic groups, with respect to the prevalence of smoking, obesity, MetS, or diabetes. However both diagnostic groups had a prevalence of cardiovascular risk factors about twice that of the general population.⁴⁸

The prevalence of the MetS among 136 adults with schizophrenia and schizoaffective disorder who were admitted to an acute psychiatric ward in 2004 was assessed together with the socio-demographic and psycho-pharmaceutical variables in a University Hospital in Gran Canaria, Spain. The prevalence of MetS, defined according to NCEP-ATP III criteria was 36% and increased with age ($p < 0.05$). Ten year coronary risk was moderate or high in a large percentage of patients, and was associated with the use of antipsychotics.⁴⁹

Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial was used to assess the prevalence of MetS by the ATP-III and AHA criteria in patients with SMI. This was reported to be 40.9% and 42.7%, respectively. The prevalence was 51.6% and 54.2%, among women, significantly higher than for men, who had prevalence values of 36.0% ($p = 0.0002$) and 36.6% ($p = 0.0003$), respectively. Logistic regression analysis, with age, race and ethnicity as covariates, showed that men and women were 138% and 251% more likely to have MetS than matched controls from the NHANES cohort.⁵⁰

In a Belgian study of 430 patients with schizophrenia admitted to a university psychiatric hospital, the prevalence of the MetS as 28.4% (ATP-III), 32.3% (ATP-III a) and 36% (IDF), respectively, at least two-fold higher than for an age-adjusted community sample.⁵¹

Table 2
Reported prevalence of metabolic syndrome in patients with schizophrenia.

Reference	McEvoy et al. ⁵⁰	De Hert et al. ⁵¹	Birkenaeas et al. ⁴⁸	Moreno et al. ⁴⁹	Huang et al. ⁵⁷	Sugawara et al. ⁵⁸	Yazici et al. ⁵⁶	Lee et al. ⁵⁹	Sweilheh et al. ⁶¹	Grover et al. ⁵²	Nyboe et al. ⁵⁴	Garcia-Rizo et al. ⁵³	Seow et al. ⁶⁰
Date	2005	2006	2007	2007	2009	2010	2011	2012	2012	2014	2015	2017	2017
Country	USA	Belgium	Norway	Spain	Taiwan	Japan	Turkey	Singapore	Palestine	India	Denmark	Spain	Singapore
Setting	Baseline data from clinical trial matched with NHANESIII	IP and OP	OP and IP versus representative community sample	IP	OP and IP	IP	OP and IP	OP and IP	OP	Anti-psychotics	Baseline data from inter-vention trial	IP	IP
N	14605;	430	1635; 110 BD; 18,770 C	136	650	1186 S 886 C	319	100S 300C	250	143	99FES 50 C	84 psychosis 98 C	108
Age group			18–65	>18	>18	>18	18–75	>21	>16	>20	FES CS	FES CS	>21
Design	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS	FES CS	FES CS	CS
MS definition	ATPIII ATPIIla	ATPIII ATPIIla IDF	ATPIII	ATPIII	ATPIII For Asians	ATPIIIa	ATPIII ATPIIla IDF	AHA	ATPIII	IDF	IDF	ATPIIIa AHA	
%MS													
Control		14	29.7	36.0	34.9	~13.0	34.2	~16	43.6	36.4		4	26.9
Schizophrenia	40.9 42.7	28.4 32.3 36				27.5	37	46				6	51.9
BD			21.5				41.7						

AHA = American Heart Association; ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III; ATPIIla = adapted ATP-III; BD = Bipolar Disorder; CS = Cross-sectional; FES = First episode schizophrenia; IDF = International Diabetes Federation; IP = In patient; MS = Metabolic syndrome; OP = Out-patient; PTSD = post-traumatic stress disorder; SMI = severe mental illness.

Of 143 patients (older than 20 years) with schizophrenia admitted to an inpatient unit, fifty-two (36.4%) patients fulfilled the criteria for MetS. These patients also had a high prevalence of cardiovascular risk factors.⁵²

Because of the potential for anti-psychotic drugs to alter the component features of MetS, prevalence studies have been undertaken in patients with a first episode of schizophrenia (FES). These patients were found to have a wide range of metabolic abnormalities. Although patients with FES (n = 84) showed a similar prevalence of MetS as a matched control sample (n = 98) (6% vs. 4%), measures of glucose homeostasis differed significantly (14% vs. 5%, $P = 0.034$). This suggests that abnormal glucose homeostasis may be an early marker for the onset of MetS in this group; MetS may not develop until the initiation of pharmacological treatment with antipsychotics, or with advancing age.⁵³ These data are consistent with another study on patients with FES in which the changes and predictors of MetS were monitored during the year following the initiation of treatment. MetS was defined according to IDF criteria. Baseline prevalence of MetS in the FES patients was higher than in controls but did not attain significance ($p = 0.07$); however, metabolic and anthropometric parameters were significantly higher: WC ($p < 0.01$), TG ($p < 0.01$), HDL ($p = 0.017$), and fasting glucose ($p = 0.04$). The increased prevalence of MetS at follow-up was significant ($p = 0.03$). Treatment with antipsychotics and low physical activity were significantly related with these changes in metabolic abnormalities.⁵⁴

A comparison has been made of the prevalence of diabetes mellitus (DM) in patients with schizophrenia attending a community mental health centre, with controls drawn from the same metropolitan area. The effects of antipsychotic exposure on the prevalence of diabetes mellitus were also investigated. These patients were found to have a higher average BMI than the controls (32.11 vs 27.62 kg/m²), a significantly higher percentage of obesity (58.5% vs. 27%, $P < 0.001$) and a significantly higher prevalence of DM (23.9% vs. 12.2%). This remained significant even after controlling for age sex, race, and for obesity (OR = 1.82, $P = 0.001$). The distribution of antipsychotic dosage, second generation antipsychotic (SGA) use or multiple antipsychotic use within different BMI categories or with diabetes status did not have a significant impact in the schizophrenia group, and the authors therefore suggest that antipsychotics may not be the only contributor to this risk of DM.⁵⁵

A cross-sectional study, of 319 Turkish patients (aged 18–75 years), with a diagnosis of schizophrenia, reported that 34.2% patients met the ATP-III criteria, 37% the ATP-IIIa and 41.7% the IDF criteria for MetS. Patients with MetS had a later onset of illness and were older at the time of first hospitalization. The prevalence of MetS in the schizophrenia patients was higher than for the general population, but only significantly so within the 20–29 age group.⁵⁶

Among 650 patients with schizophrenia or schizoaffective disorder recruited from 36 psychiatric institutions in Taiwan, the prevalence of MetS was 34.9% (38.9% in women and 31.5% in men respectively), based on the modified ATPIII criteria for Asians. The difference in MetS prevalence between the patient sample and the general population was marked in male patients under 40 years of age and in female patients under 50 years old. A BMI ≥ 24 and age ≥ 40 years old were important risk factors for MetS. Female gender and poly-pharmacy were marginally significant factors in this population sample.⁵⁷

MetS prevalence was assessed among 1186 Japanese patients with schizophrenia or schizoaffective disorder and 886 controls. The patients were recruited from seven psychiatric hospitals, and MetS, was defined using three different definitions, including the ATP IIIa definition. The total prevalence of MetS, based on the ATP IIIa definition was 27.5% (29.8% in male and 25.3% in female patients). Logistic regression analysis showed that the presence of

schizophrenia was a significant independent factor (odds ratio = 2.00 for males, 2.13 for females) for the development of MetS.⁵⁸

In a sample of 100 patients with schizophrenia and 300 community controls from Singapore, the prevalence of MetS in patients with schizophrenia was reported to be 46.0%. The adjusted odds ratio for MetS among patients was 2.79 (CI, 1.50–5.20, $P = 0.001$) when compared with controls.⁵⁹ A further study from Singapore determined the cardio-metabolic risk profile and the associated risk factors for a group of institutionalized patients with schizophrenia or schizoaffective disorder receiving prolonged hospital care. The prevalence of MetS in this group was 51.9% and 26.9% based on the AHA/NHLBI and modified NCEP ATP III criteria respectively. 10-year cardiovascular risk was estimated at 12.8%, indicating an intermediate risk based on the Framingham risk algorithm. There was no significant association with the use of atypical antipsychotic drug therapy and the duration of hospitalization did not affect the rate of MetS in this sample.⁶⁰

The prevalence of MetS was investigated among patients with schizophrenia in Palestine. Two hundred and fifty patients with schizophrenia were recruited from 4 psychiatric primary health-care centres in Northern Palestine. The presence of MetS was assessed based on ATPIII criteria. The overall prevalence of MetS was 43.6%, (39% of men and 55.9% of women). Univariate analysis showed that MetS increased significantly with age, female gender, longer duration of the illness, a positive smoking habit, abdominal obesity, high systolic and diastolic blood pressure, high triglycerides, low HDL-C, and high fasting plasma glucose.⁶¹

A large Japanese study involved the recruitment of 7655 outpatients and 15,461 in-patients with schizophrenia, who were recruited from 520 outpatient facilities and 247 inpatient facilities of the Japan Psychiatric Hospitals Association between 2012 and 2013. The outpatients had significantly higher prevalence of obesity, hypertension, hypertriglyceridemia, high-LDL-C, and DM than the inpatients. The prevalence of low-HDL-C was higher in inpatients than outpatients. Age-specific analysis showed the prevalence of obesity, hypertension, hypertriglyceridemia, high-LDL-C, and DM among outpatients to be 2–3-fold-higher than among inpatients. In individuals aged ≥ 60 years, the prevalence of obesity and DM among outpatients was about 3-fold higher than among inpatients.⁶²

Serum uric acid (UA) is derived from purine metabolism, and hyperuricaemia may be associated with gout. Gout itself is associated with an increased risk of CVD,⁶³ but hyperuricaemia has also been frequently reported to be associated with MetS in population studies.⁶⁴ However, there appear to be differences in this association between genders and ethnicities.⁶⁵ Serum UA has been found to be reduced in patients with schizophrenia,⁶⁶ and this has been attributed to altered purine catabolism and treatment with antipsychotics⁶⁷; but serum UA has been reported to be raised in patients with bipolar disease.⁶⁸ In an Asian study, 637 patients (342 male) were recruited from 36 psychiatric rehabilitation institutions. Serum UA concentrations were positively associated with hypertriglyceridemia, low high-density lipoprotein cholesterol level, and high blood pressure in men and with hypertriglyceridemia in women. In men with schizophrenia or schizoaffective disorder lower concentrations of serum uric acid were associated with lower risk of MetS.⁶⁹

The assessment of central adiposity is an important feature for defining MetS. A cross-sectional study of 382 inpatients with schizophrenia-related disorders assessed the prevalence of each component of MetS. In this analysis, WC was measured at several sites. Logistic regression analysis was used to assess the ability of WC at each site to predict the presence of metabolic risk clustering. The site of measurement of WC influenced the estimated

prevalence of abdominal obesity (30–38.2% in men and 53.9–86.3% in women) and of MetS. The areas under the ROC curve for metabolic risk clustering were highest for the measurement of WC at the umbilicus and midpoint.⁷⁰

High sensitivity C-reactive protein (hs-CRP) is a serum inflammatory marker synthesised in the liver and positively associated with CVD and mortality.⁷¹ Serum hs-CRP levels were reported to be significantly higher in individuals with schizophrenia than in healthy control subjects, and its levels were associated with more severe symptoms, greater medical co-morbidity, and metabolic risk factors, including BMI, and fasting glucose, that were also more severely disturbed.⁷²

Hence schizophrenia is associated with an increased risk of CVD and/or MetS in European and Asian populations. It is also associated with other features of MetS, including hyperuricaemia and raised serum hs-CRP, both of which are also risk factors for CVD. Abnormalities in glucose homeostasis are evident in FES, before treatment with antipsychotics has started, and therefore there are likely to be other contributors to the risk of DM and MetS apart from the use of anti-psychotic drugs in these patients.

4. Prevalence of metabolic syndrome and associated features in patients with bipolar disorders [Table 3]

BD is an episodic mood disturbance with a chronic course and multisystem involvement. Disturbances of circadian rhythms, mood instability, cognitive impairment, and a high rate of medical co-morbidity are often observed. BD is also associated with a high prevalence of psychiatric comorbidity and an increased mortality from physical disease,⁷³ particularly in older patients.⁷⁴ Whilst there is a high prevalence of comorbid physical and psychiatric disorders in patients with BD; these do not appear to affect the relapse risk in patients with BD, they may however further enhance the risk of MetS.⁷⁵

In an early report, the point prevalence of MetS, defined using WHO criteria was determined in 33 patients with schizoaffective disorder-bipolar type, who were recruited into a clinical drug trial, was reported to be higher than for the general population of the USA.⁷⁶

In studies of cardiovascular and all-cause mortality, BD has been associated with an approximate doubling of risk in both men and women compared to general population estimates, and an 8–9 year reduction in lifespan.² This may be partly explained by the elevated burden of CVR factors found in this population, and these early findings predate modern treatments for BD, which may further exacerbate CVR.⁷⁷ Suicide risk has been reported to be 10-fold among women and 8-fold among men with BD, compared with the rest of the population.²

The cardiovascular mortality among people with BD compared to the general population in Sweden was investigated using a population register-based cohort study with a 20-year follow-up. The entire population of Sweden ($n = 10.6$ million) was included, of whom 17,101 individuals were diagnosed with BD between 1987 and 2006. Individuals with BD died of CVD approximately 10 years earlier than the general population. Despite the increased mortality from CVD, hospital admissions for CVD treatment were only slightly increased in people with BD when compared to the general population.⁷⁸

In a European cross sectional study, the prevalence of MetS among patients with BD was assessed using ATP-III, the ATP-IIIa criteria using a fasting glucose threshold of 100 mg/dL, and the most recently proposed criteria from the International Diabetes Federation (IDF). The prevalence of MetS was of 16.7% (ATP-III), 18.3% (adapted ATP-III) and 30.0% (IDF), respectively.⁷⁹

Table 3

Reported prevalence of metabolic syndrome in patients with bipolar disease and depression.

Reference	Basu et al. ⁷⁶	Bermudes et al. ⁹⁸	Van Winkel et al. ⁷⁹	Chang et al. ⁸¹	Guan et al. ⁸³	Lee et al. ⁸⁴	Ezzaher et al. ⁸²	Kim et al. ¹⁰⁰	Lasserre et al. ⁹⁷
Date	2004	2006	2008	2009	2010	2010	2011	2015	2017
Country	USA	USA	Belgium	Taiwan	China	Korea	Tunisia	Korea	Switzerland
Setting	Drug trial	IP	OP and IP	OP	OP and IP	OP	OP and IP	OP	OP
N	33	122	60 majority on Anti-psychotics	117 treated with valproate, lithium or both	148 BP 65 C	152 BP	130, >70% treated with mood stabilizers	13,745	2813
Age group	>21	>18	>21	>21	>21	>21	>18	40–59	35–66
Design	CS	CS	CS	CS	CS	CS	CS	Cohort Study	Cohort Study
MS definition	WHO	ATPIII	ATPIII ATPIIIa IDF	IDF	Chinese Med Assoc	ATPIII AHA IDF	ATPIIIa		
%MS									
Control						~10.0			
Depression		38.6		33.9	11.5	25.0	26.1		
BD	42.5		16.7 18.3 30.0			27.0 25.7			

AHA = American Heart Association; ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III; ATPIIIa = adapted ATP-III; BD = Bipolar Disorder; CS = Cross-sectional; IDF = International Diabetes Federation; IP = In patient; MS = Metabolic syndrome; OP = Out-patient; PTSD = post-traumatic stress disorder; SMI = severe mental illness.

A systematic review has reported that the prevalence of MetS in BD was significantly higher than in the general population (between 36 and 49% in the USA), and could be explained by several determinants, including reduced physical activity and poor diet, genetic susceptibility, psychiatric comorbidity and anti-psychotropic treatment. Patients with BD have disturbances of the circadian cycle and sleep. These latter disturbances are known to persist even during periods of mood stabilization and are found in the relatives of these patients, suggesting a genetic contribution to sleep disturbance. The circadian and sleeping disorders may affect the prevalence of MetS in BD, possibly due to a linkage to leptin and ghrelin dysregulation. Prevention and treatment of circadian disorder in BD may reduce the occurrence of MetS in these patients.⁸⁰

A high prevalence of obesity and metabolic disturbances have been reported in patients with BD in Western countries, although there have been few studies in Asian countries. A cross-sectional study of 117 patients diagnosed with BD and treated with lithium, valproate, or both was undertaken at a University psychiatric outpatient clinic in Taiwan. It was found that 33.9% of the patients met the IDF 2005 criteria for MetS. The prevalence of metabolic abnormalities was significantly higher in patients who were co-treated with second-generation antipsychotics (SGAs).⁸¹

The prevalence of MetS in Tunisian patients with BD (n = 130) was assessed for MetS according to ATPIII modified criteria, and was found to be 26.1%. The highest prevalence of MetS was associated with obesity, low HDL-C and hypertriglyceridemia (44.1%). Patients treated with lithium had a higher prevalence of MetS than those treated with valproic acid (VPA), carbamazepine or antipsychotics.⁸²

The prevalence of MetS and its correlates was also investigated in patients with BD from southern China, during their acute-phase of treatment. The study included 148 patients with BD presenting with acute mood symptoms and 65 healthy controls. Chinese Medical Association Diabetes Branch criteria were used to define MetS. MetS prevalence rates were calculated at entry and recalculated for patients after months 1, 3, and 6. At baseline, MetS was found in 11.5% of the patients; overweight in 34.5%; low high-density lipoprotein cholesterol in, 15.5%; hypertriglyceridemia in 29.1%; hypertension in 14.9%; and hyperglycemia in 5.4%. Compared with controls, the patients had a significantly higher prevalence of MetS and all its components apart from

hyperglycemia ($P < 0.05$). In the regression analysis, a history of hypertension, presence of diabetes, and alcohol consumption were associated with the presence of MS.⁸³

Korean patients with BD were investigated to assess the comorbidity of BD with MetS, and to compare the prevalence of MetS in patients on medication for BD with that of healthy patients in Seoul National University Hospital between 2007 and 2008. The control group, matched for age and gender, was randomly drawn from visitors to the Health Promotion Centre at the same hospital during the same period. The prevalence of MetS in patients who took medication for BD was 27.0%, 25.0% and 25.7%, based on the definitions of the American Heart Association and the National Heart, Lung and Blood Institute's adaptation of the ATP IIIa, the ATPIII and the IDF, respectively. The prevalence of MetS was significantly higher in patients with BD than in the control group. Patients on medications for BD showed a significantly higher prevalence of increased waist circumference, elevated triglyceride, and lower HDL-cholesterol than the controls. Obesity and dyslipidaemia were particularly prevalent in patients with BD.⁸⁴

It is therefore apparent that MetS and BD share common risk factors, including endocrine disturbances, dysregulation of the sympathetic nervous system, and altered behaviour patterns, such as sedentariness and overeating. This may partially account for the increased risk of hypertension in BD, reported by Ayerbe et al. in their meta-analysis.⁸⁵ Many of the commonly used drug treatments for BD may further exacerbate weight gain and metabolic disturbances in bipolar patients by causing alterations in lipid and glucose metabolism, which can result in an increased risk for DM, hypertension, dyslipidaemia, CVD and MetS. A recent meta-analysis also suggests that antidepressant use is associated with new onset DM.⁸⁶ These co-morbidities may be associated with the premature mortality observed in bipolar patients. Furthermore, weight gain is also a major cause of treatment non-compliance, and an increased use of clinical services.⁸⁷

There appear to be gender effects that determine the risk of dyslipidaemia and IR in patients with BD. In a study of 491 outpatients (ages 18–88) attending the Stanford Bipolar Disorders clinic between 2000 and 2007, women had a significantly lower prevalence of dyslipidaemia than men.⁸⁸

Serum C-Reactive Protein (CRP) and homocysteine are both independent risk factors for CVD. A meta-analysis comprising 11 studies and 1618 individuals showed that serum CRP

Table 4

Reported prevalence of metabolic syndrome in patients with other serious mental illness and on treatment with antipsychotics.

Reference	Linnville et al. ¹⁰⁹	Heppner et al. ¹⁰⁸	Elmslie et al. ¹²⁵	Margari et al. ¹²²	Ojala et al. ¹¹⁶	Taylor et al. ¹²⁹	Brunero et al. ¹¹⁹	Correll et al. ¹¹⁷	Krane-Gartiser et al. ¹¹⁸	Correll et al. ¹²⁷	Saddichha et al. ¹³¹	Vandenberghe et al. ¹⁴²	Popovic et al. ¹⁴³	Munshi et al. ¹¹⁴	Lin et al. ¹¹⁵	Eskelinen et al. ¹⁴⁴
Date	2011	2009	2009	2013	2008	2010	2009	2006	2011	2008	2008	2015	2015	2015	2015	2015
Country	USA	USA	New Zealand	Italy	Finland	Canada	Australia	USA	Denmark	USA	India		Serbia	Canada	Taiwan	Finland
Setting	OP	OP	OP		Forensic Psychiatry IP	IP	OP	IP	OP	IP			IP		IP	OP
N	351 veterans with no other Psychiatric Co-morbidity	233 veterans Mostly male and white	60 BD on val-proate 60 non-psychiatric controls	83 Schizophrenia 24 BD 27 MDD 14 Other 18 77 C internal med >21	221	54 Mania or Depression 104 NHANESIII control data	73 patients on clozapine	367	170 Patients on anti-psychotics 3303 controls	111 Schizophrenia 74 BD On anti-psychotics	99	351	93 patients with schizophrenia on treatment with olanzapine	50 patients 80% on SGA	329 patients with schizophrenia on SGA	276 patients with schizophrenia High % on clozapine
Age group	>50															
Design	CS but 25 years after initial recruitment	CS	Matched Control CS			16–40 Matched control Cohort			Matched control CS		DB Controlled trial		>21 CS case–control	CS	CS	CS
MS definition	ATPIIIa	ATPIII				ATPIII	IDF		IDF	ATPIII ATPa	ATPIIIa IDF		IDF	IDF	IDF	IDF
%MS Control	25		32			Baseline 19 Follow-up 14	62		29.6					48		
SMI												22 at baseline				
Schizophrenia										45.9 54	10 18				23.7	58.7
NA Psychosis																
Aff Psychosis																
Depression		29				Baseline 15 follow-up 17										
BD			50			Baseline 5 follow-up 15				43.2 54						
PTSD	25	34 (46 if plus MDD)														
Anti-Psych								37	48			32 after 1 year on treatment	34.4			

AHA = American Heart Association; ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III; ATPIIIa = adapted ATP-III; BD = Bipolar Disorder; CS = Cross-sectional; FES = First episode schizophrenia; IDF = International Diabetes Federation; IP = In patient; MS = Metabolic syndrome; OP = Out-patient; PTSD = post-traumatic stress disorder; SMI = severe mental illness.

concentrations are significantly raised in patients with BD and unrelated to drug treatment.⁸⁹ In 122 patients with bipolar ($n = 60$) and schizophrenia ($n = 62$) treated with second-generation antipsychotics (SGA) and healthy controls ($n = 59$), the prevalence of MetS (using ATP-III criteria) was associated with hyperhomocysteinaemia, which conferred a >8 fold risk of MetS.⁹⁰

5. Prevalence of metabolic syndrome and associated features in patients with depression [Table 4]

Depression is associated with an increased risk of premature death, death from unnatural causes⁹¹ and CVD.⁹² In a review reporting on the MetS prevalence in major depressive disorders (MDD), MetS was found in approximately 30.5% of patients using any of the standardized MetS criteria. This was approximately 1.5 fold that for age- and gender-matched controls. Antipsychotic use was a significant determinant of the increased prevalence of MetS ($p < 0.05$), whereas age, gender, geographical area, smoking habit, antidepressant use, and presence of psychiatric co-morbidity, were not.⁹³ Patients with a long history of depressive symptoms have a lower serum HDL-C and higher atherogenic lipid indices compared with healthy controls.⁹⁴ In a cross-sectional study of 133 older people, Viscogliosi et al. found that the presence of MetS and serum hs-CRP were independently associated with depressive symptoms.⁹⁵

The CoLaus/PsyCoLaus prospective cohort study showed that an atypical form of MDD⁹⁶ was prospectively associated with a higher incidence of the MetS and a steeper rise of fasting glucose during follow-up. Perhaps surprisingly these associations were found not to be due to eating behaviours, comorbid psychiatric disorders or lifestyle factors.⁹⁷

The prevalence of the MetS in a recent survey of psychiatric inpatients with severe mood and psychotic disorders, showed that among 102 consecutively adult patients admitted with a primary diagnosis of a mood or psychotic disorder, the prevalence of MetS was 38.6%, and was associated with increasing age, body mass index, and Caucasian ethnicity.⁹⁸

A cross-sectional study of adult patients with depression found that the prevalence of overweight and obesity was 72% in patients with longer duration of disease, also being associated with a higher BMI and percentage fat mass. Weight gain during the illness was found in 87% of patients; and was at least partially attributable to: a poor diet, with a regular consumption of high calorie foods; the use of anti-in these patients depressants and benzodiazepines, and insufficient physical activity.⁹⁹

In a retrospective cohort study included 13,745 subjects (8113 men and 5632 women) 40–59 years of age who were investigated at the Seoul National University Hospital Healthcare System, in Korea. The median follow-up duration was 4.0 years. Four distinctive trajectories of depressive symptoms were identified, that were present in both genders. There was a significant increasing trend in the prevalence of metabolic abnormalities in those patients with a more severe trajectory of depressive disease, and this was also associated with MetS.¹⁰⁰

Both MDD and the MetS are associated with a genetic susceptibility and impaired serotonergic neurotransmission in specific areas of the brain. The variants in the genes encoding tryptophan hydroxylase 2 (TPH2) (the brain-specific and rate-limiting enzyme for serotonin biosynthesis), was investigated in 988 patients with recurrent unipolar depression and 1023 psychiatric healthy controls. TPH2 polymorphisms were found to define a sub-group of depressed patients who may be susceptible to developing metabolic disorders. The authors propose that this may be induced by a genotype-dependent impairment of serotonergic neurotransmission.¹⁰¹

A small cross-sectional study of patients with chronic MDD, acute MDD and controls, reported that the patients with chronic MDD had highest volumes of pericardial adipose tissue (PAT).¹⁰² PAT volume has been implicated in the development of coronary artery disease, and was found to be positively associated with adrenal gland volume. Patients with chronic MDD also had the higher prevalence of MetS and levels of serum cortisol and pro-inflammatory cytokine concentrations. Hence, the hypothalamus–pituitary–adrenal axis may have a central role in the relationship between chronic MDD and coronary artery disease.

The numbers of studies on the effects of antidepressants on the features and prevalence of MetS are limited. Using data from the Hordaland study, Raeder et al. found that some selective serotonin re-uptake inhibitors (SSRIs), for example paroxetine, were associated with abdominal obesity.¹⁰³ Dordland and colleagues have reported that the use of tricyclic antidepressants are also associated with the risk of MetS independently of the severity of depression.¹⁰⁴ A large French cohort study reported the risk of MetS in men and women treated with antidepressants over 9 years.¹⁰⁵ There was a significantly higher risk of MetS in men but not women, and for those taking SSRIs.

6. Metabolic syndrome in patients with post-traumatic stress [Table 4]

Post-traumatic stress disorder (PTSD) is a mental disorder that may arise following exposure to a traumatic event, that may be physical (e.g. war injury), or psychological (sexual abuse), and leads to disturbed thoughts and dreams, and physical and mental distress in response to particular cues.¹⁰⁶ PTSD is associated with somatic disease and a shortened lifespan, and obesity, dyslipidaemia, hypertension, DM, and CVD are prevalent among patients with PTSD.¹⁰⁷ In patients with combat-related PTSD, who developed MetS, there were higher rates of anxiety, depression and recent life changes scores compared to those without.¹⁸ Among 253 veterans from the USA, a high prevalence of MetS was found in those with PTSD alone (34%), MDD alone (29%), and particularly those with PTSD and MDD combined (46%).¹⁰⁸ The rates of MetS were reported to be particularly high in those with more severe PTSD.

In contrast, a retrospective analysis of metabolic data for Vietnam-era repatriated prisoners of war (RPWs) found that the prevalence of MetS was the same in RPWs with and without PTSD and a comparator group. Moreover, PTSD symptom severity did not increase the likelihood of MetS in this study.¹⁰⁹ However this latter study excluded individuals with other psychiatric co-morbidities.

The potential effects of antipsychotic drug usage, particularly SGAs on the risk of MetS and obesity, may account for some if not all of the observed metabolic problems in PTSD. A cross-sectional study investigated this in veterans enrolling in mental health services. Antipsychotic medication usage was not associated with elevated risk of MetS when PTSD severity and other socio-demographic, psychiatric, and behavioural variables were accounted for. PTSD severity continued to be a significant and unique predictor of risk for MetS ($p < 0.05$).¹¹⁰

7. Prevalence of metabolic syndrome in patients with substance dependency

Individuals with alcohol use disorders (AUDs) have an increased risk for CVD and associated premature mortality. MetS and its components were investigated in a meta-analysis of people with AUDs taking into account variations in demographic and clinical variables. The pooled MetS prevalence after adjusting for publication bias was 21.8%; abdominal obesity was observed in 38.3%, hypertriglyceridemia in 43.9%, low high-density lipoprotein

cholesterol in 7.6% and hypertension in 46.5%. A meta-regression analysis showed that a higher MetS frequency was associated with a higher frequency of psychiatric co-morbidities.¹¹¹

8. Stress and metabolic syndrome and its components

Stress may cause some people to eat less and lose weight and others to eat more. Using longitudinal data, the effects of work-related stress was assessed in the Whitehall II study cohort, comprising 5547 men and 2418 women, aged 35–55 at entry. Work stress, assessed using a job strain model, and measured as job control, job demands and job strain, was assessed at baseline and BMI at baseline and at 5-year follow-up. In men, the effect of job strain on weight gain and weight loss was dependent on baseline BMI ($P < 0.03$). In the leanest quintile ($\text{BMI} \leq 22 \text{ kg/m}^2$) at baseline, high job strain and low job control were associated with weight loss, whereas among those in the highest BMI quintile ($\text{BMI} > 42.7 \text{ kg/m}^2$), these stress indicators were associated with weight gain. The interaction was not seen among women.¹¹²

In a cross-sectional study of 1822 obese outpatients seeking treatment in medical centres, health related quality of life (HRQL) was measured by summary scores for physical (PCS) and mental (MCS) components of the Short Form 36 Health Survey (SF-36). Patients were grouped according to tertiles of PCS and MCS. Metabolic and psychological profiles of tertiles for PCS and MCS were compared by discriminant analysis. The main correlates of PCS were obesity-specific and general psychological well-being, BMI, binge eating, gender and psychiatric distress. Hypertension and hyperglycemia were significant correlates among the components of MetS. Features of MetS correlate with the physical domain of HRQL to some degree.¹¹³

9. Effects of antipsychotic drug treatment on the risk of metabolic syndrome

The use of atypical antipsychotic drugs in patients with psychiatric illness may result in dyslipidaemia, hypertension, glucose intolerance, and abdominal obesity. This has been investigated using cross-sectional, case–control and cohort studies.

9.1. Cross-sectional studies

In an acute care psychiatry inpatient unit at Kingston General Hospital, Ontario, Canada, and comprised adult patients of both genders diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. MetS was defined using the IDF criteria. Of the 50 patients in the study, 24 (48%) were found to have MetS, of whom 83% were taking atypical antipsychotics and 20 (77%) among those were not on these drugs.¹¹⁴

Three hundred and twenty nine Han Chinese patients were recruited from a psychiatric hospital in central Taiwan. Using the definitions of the IDF for Chinese, the prevalence of MetS was 23.7% (men: 25.7%; women: 21.2%). An abnormal non-HDL-C was a significant risk factor for men with MetS (OR: 4.127, $p < 0.001$), but not for women. There was a greater prevalence of MetS in patients with schizophrenia taking SGAs than in the general population.¹¹⁵

The prevalence of MetS and its risk determinants was investigated among 221 Finnish psychotic forensic psychiatric inpatients with comorbidities of antisocial personality or alcohol dependence. Schizophrenia, or a related psychosis was the predominant diagnosis (92%), and these patients had been on constant SGA medication for the previous over six months. The use of clozapine (OR 8.1), quetiapine (OR 7.7), and olanzapine (OR 3.6) was associated with an increased occurrence of MetS. A beneficial high-density lipoprotein cholesterol profile was found with the use of selective

serotonin uptake inhibitor (SSRI), and with a diagnosis of alcohol dependence, even after alcohol abstinence. MetS was associated with the use of clozapine and quetiapine.¹¹⁶

Three hundred and sixty seven adults treated with second-generation antipsychotics randomly selected from consecutive psychiatric admissions to a single hospital, underwent assessments evaluating the presence of MetS. MetS, was found in 137 patients (37.3%), and was associated with a significantly greater age- and race-adjusted 10-year risk of CHD events, i.e., 11.5% vs. 5.3% for men and 4.5% vs. 2.3% for women.¹¹⁷

The prevalence of the MetS in an Outpatients psychiatric clinic in Denmark, was compared to the general population in 2007–2008, 170 Danish outpatients on antipsychotic drug treatment were assessed for the prevalence of the MetS based on the IDF definition and compared with a general population of 3303 randomly selected Danes. Of the antipsychotic-treated patients, 48.2% fulfilled the IDF criteria for the MetS, compared with 29.6% of the general population. The antipsychotic-treated patients had higher rates of increased waist circumference, triglyceride and glucose levels, and lower high-density lipoprotein cholesterol. The odds ratio (OR) of the MetS among patients treated with antipsychotics was 2.2. After adjustment for age and sex, the OR increased to 2.7. There were statistically different rates of the MetS for patients on mono-pharmacy vs. poly-pharmacy, and for patients on mono-therapy with first-generation vs. second-generation antipsychotics.¹¹⁸

The prevalence and predictors of MetS were studied in patients attending an outpatient clozapine clinic in Australia: Seventy-three patients were screened for MetS using the IDF (2007) definition, 61.6% patients met the criteria for the syndrome.¹¹⁹

A recent study has reported that serum CRP levels are higher in patients treated with some atypical antipsychotic medications such as olanzapine; however, it was unclear whether this was directly associated with drug intake, or indirectly related to drug-associated weight gain and insulin resistance. Sixty-four outpatients without diabetes being treated with a single second generation antipsychotic medication was investigated. IR was the strongest predictor of serum CRP ($r = 0.52$, $P < 0.001$), and after adjustment for this there was no significant relationship between CRP and any of the components of the MetS.¹²⁰

9.2. Case-control studies

The metabolic profiles of patients with schizophrenia taking atypical antipsychotics were compared to their siblings, and controls ($N = 50$ in each group). Patients with schizophrenia had a significantly higher body mass index, waist circumference, and insulin resistance, and showed a trend toward a difference in glucose levels.¹²¹

Eighty-three psychiatric in-patients under pharmacological treatment (schizophrenia, $n = 24$, BD, $n = 27$, MDD, $n = 14$, and other, $n = 18$) were compared with 77 internal medicine patients. Triglycerides and triglycerides/HDL ratio were higher in the patients with MDD. A positive association was found between antidepressant drug treatment and triglycerides and triglycerides/HDL ratios, neuroleptic treatment with the Homeostatic model assessment (HOMA) index, and antipsychotics drugs with the overall Framingham risk score.¹²²

In a case–control study of 90 people treated with antipsychotics in the community and 92 age- and gender-matched controls, the prevalence of MetS and 10-year cardiovascular risk were compared. Treatment with antipsychotics was associated with a significantly worse metabolic profile than controls ($P < 0.0001$), and MetS was more prevalent ($P = 0.001$), as was a high CVD risk across a number of outcomes. This was consistent across diagnostic categories.¹²³

Metabolic abnormalities in patients with BD may be secondary to obesity, aspects of the disorder itself, or its treatment. A comparison was made with respect to IR, features of the MetS and serum adiponectin levels in a group of overweight BD patients taking sodium valproate and a group of non-psychiatric control subjects matched for age, gender, BMI and ethnicity. Adiponectin is a hormone derived from adipose tissue that modulates glucose and fatty acid oxidation.¹²⁴ The frequency of the MetS was high in both groups (50% and 32%, respectively), although this was not significantly different between groups ($p = 0.06$). Similar frequencies of insulin resistance (HOMA-IR), abdominal obesity, hypertriglyceridaemia, hypertension and fasting hyperglycaemia were found in both groups. High-density lipoprotein cholesterol levels were lower in patients ($p = 0.006$). Serum adiponectin concentrations were unexpectedly found to be higher in the BD patients compared to the control subjects. The frequencies of insulin resistance [defined using HOMA-insulin resistance (IR)], MetS and its individual components were not significantly different in patients taking atypical antipsychotic medication and patients not on these medications. Frequencies of IR and MetS were similar in bipolar patients taking sodium valproate and matched control subjects, but dyslipidaemia was more frequent.¹²⁵

The metabolic status among VPA treated BD patients; drug-free BD patients (BD-F) and healthy controls were investigated in a Taiwanese population. The cross-sectional study included 119 healthy controls and 77 BD patients diagnosed according to the DSM-IV-TR criteria. VPA treatment was associated with significantly higher plasma insulin, triglyceride, and BMI levels as well as lower fasting glucose and HDL levels. However, these biochemical indices did not differ significantly between the BD-F and the healthy control groups. Hence, treatment with VPA may increase the risk of metabolic disturbances in patients with BD.¹²⁶

The prevalence of MetS in patients with BD and schizophrenia patients receiving SGAs were compared. Patients treated with SGAs were closely matched for age, sex, and race. Compared to schizophrenia patients those with BD had lower BMI, were more likely to have been treated with mood stabilizers, and less likely to have been treated with clozapine. Despite these differences, BD and schizophrenia patients had comparable rates of MetS (43.2% versus 45.9%, $p = 0.71$) and predicted CHD events (10-year risk > 10%: 18.9% versus 23.4%, $p = 0.47$). Using 100 mg/dL as the adapted glucose criterion, MetS rates were 54.0% in both patient groups ($p = 1.0$). Mood stabilizer co-treatment was not associated with MetS or its individual criteria. The authors suggest that these findings indicate a shared susceptibility to antipsychotic-related metabolic dysregulation that is not primarily related to psychiatric diagnosis or concomitant mood stabilizer treatment.¹²⁷

Serum leptin, adiponectin and paraoxonase1 (an antioxidant enzyme present on the HDL particle) levels were investigated in women receiving pharmacotherapy for various psychiatric disorders. A small study compared 32 obese women who were receiving treatment for psychiatric disorders, and a control group of 22 obese females who were free from psychiatric disorders. BMI and hip circumference were positively related with serum leptin levels, hip circumference correlated positively with adiponectin levels, and waist to hip ratio correlated positively with serum paraoxonase levels. In the control group, BMI as well as waist and hip circumferences were positively correlated with leptin levels. Weight, BMI, and hip circumference were also negatively correlated with the adiponectin/leptin ratio in the control group. The authors concluded that there appears to be a higher risk for obesity-related disorders in patients treated with psychiatric drugs.¹²⁸

9.3. Cohort studies

The incidence of MetS was determined for newly diagnosed patients with MDD ($n = 30$) and BD ($n = 24$). At baseline, 11.2% of patients met diagnostic criteria for MetS and this increased to 16.8% at follow-up. Women had higher rates of MetS but rates were similar across diagnoses. In this study, changes in CHD and MetS risk were not associated with a specific type of pharmacotherapy, as all medication classes appeared to increase risk.¹²⁹

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study provided further evidence of the metabolic risk associated with different atypical antipsychotics. Based on data from this and other studies, it was concluded that clozapine and olanzapine treatment can produce substantial changes in weight and an increased risk of associated metabolic disturbances. Risperidone and quetiapine treatment may produce moderate changes in mean weight in comparison to treatment with other atypical antipsychotics. Aripiprazole and ziprasidone treatment may induce the lowest mean changes in weight gain and has been reported to have no effect on risk for adverse metabolic changes, among currently available atypical agents.¹³⁰

Consecutive patients with FES in India were recruited into a prospective randomized, double blind controlled study and randomized to receive either, haloperidol, olanzapine or risperidone. The prevalence of MetS was assessed based on two criteria- ATP IIIA and IDF criteria. This was compared with a gender, age, exercise and diet matched healthy control group. The prevalence of MetS was 10.1% and 18.2% as assessed by ATP IIIA and IDF criteria respectively. The prevalence of MetS in patients with schizophrenia was at least five times higher than for a matched healthy control group. Olanzapine increased the prevalence of MetS to between 20 and 25%, risperidone to 9–24% and haloperidol to 0–3%.¹³¹

Weight gain among inpatients that received antipsychotic drug therapy was compared in patients treated with first and SGA therapy for one year or longer (risperidone $N = 40$; olanzapine $N = 30$). The control group included 30 patients who were treated with first generation antipsychotics. Following one year of treatment 55% of the patients gained weight, 2% remained at the same weight and 43% had lost weight. Currently there appears to be no alternative to personal follow up for each individual patient and personal treatment plans for medication, diet and physical exercise.¹³²

HOMA-IR was used in non-diabetic patients with schizophrenia treated with clozapine or olanzapine. No difference was found between the groups treated with clozapine and olanzapine with respect to age, gender, race, BMI, waist circumference (WC), or lipid levels. Nor did measures of insulin sensitivity differ between the groups (HOMA-IR, or SI).¹³³

The effects of switching from quetiapine to ziprasidone on weight, safety, and effectiveness were investigated in 241 subjects with schizophrenia or schizo-affective disorder who had been treated with quetiapine (≥ 300 mg/day) for ≥ 3 months with either sub-optimal efficacy or poor tolerability. They were enrolled into a 16-week, open-label, flexible-dose trial, with a 16-week follow-up (total 32 weeks). The primary endpoint was weight change from baseline at 16 weeks, when there was a small but statistically significant reduction in weight, with a mean change from baseline of -0.73 kg, as well as improved lipid profiles, regardless of their metabolic status and disease severity at baseline.¹³⁴

Hence there is good evidence that antipsychotic medication can increase adiposity, and this also suggests that treatment with antipsychotic medications may be associated with an increased risk for IR, dyslipidaemia, and DM. Different antipsychotic drugs appear to be associated with different degrees of treatment-induced increases in body weight and adiposity, ranging from modest effects

(<2 kg) with amisulpride, ziprasidone, and aripiprazole to clinically significant increases with olanzapine (4–10 kg). Metabolic changes in patients who receive antipsychotic agents may contribute to the development of the MetS.¹³⁵ Antipsychotic treatment may contribute to obesity by several potential mechanisms, as previously discussed.

The high prevalence of MetS in patients with BD is reported to be comparable to the prevalence of MetS in patients with schizophrenia. A small study has also investigated if the presence of MetS was associated with hyper-homocysteinaemia in patients with BD (N = 36) and schizophrenia (N = 46) treated with SGA. The presence of the MetS was significantly associated with an elevated serum homocysteine in all participants.¹³⁶

SGAs are increasingly being used to treat children with a variety of psychiatric illnesses. In a cross-sectional study, Devlin et al. assessed the association of the methylenetetrahydrofolate reductase (MTHFR) C677T gene variant with features of MetS in SGA-treated (n = 105) and SGA-naïve (n = 112) children. The MTHFR C677T variant, is associated with higher concentrations of serum homocysteine, and was chosen because it was previously reported to be associated with risk for CVD,^{137,138} although this is now contended.¹³⁹ It is also associated with features of MetS in adults without psychiatric illness. MetS was determined in children, based on the: waist circumference ≥ 90 th percentile for age and sex; plasma triglyceride ≥ 1.24 mmol/L; plasma high-density lipoprotein-cholesterol ≤ 1.03 mmol/L; systolic or diastolic blood pressure ≥ 90 th percentile for age, sex, and height; and fasting glucose ≥ 5.6 mmol/L. 15% of the children treated with SGA had MetS compared with 2% of the SGA-naïve children. The MTHFR 677T allele was associated (P < 0.05) with MetS (OR 5.75, 95% CI = 1.18–28.12) in the SGA-treated children. A positive relationship between the MTHFR 677T allele and diastolic blood pressure Z-scores (P = 0.001) and fasting plasma glucose (P < 0.05) in children treated with SGAs. There was a high prevalence of MetS in these children and a metabolic alteration associated with the MTHFR C677T variant may have a role in the development of MetS features in children treated with SGAs.¹⁴⁰

SGAs are widely used in psychiatric disease and appear to have different propensities for inducing weight gain. An analysis of the randomized-controlled trials and observational studies published between 2010 and 2014 with sample sizes exceeding 100, have been analysed to determine the ranking of SGAs with respect to affecting weight gain. Clozapine and olanzapine appear to have the highest risk, followed by amisulpride, asenapine, iloperidone, paliperidone, quetiapine, risperidone and sertindole in the middle, and aripiprazole, lurasidone and ziprasidone with the lowest risk. Younger patients and patients with a lower baseline body mass index appear to be most vulnerable. The greatest amount of weight gain occurs within the first few weeks of treatment.¹⁴¹

Data were obtained from a longitudinal study initially started in 2007, and included 351 Swiss psychiatric patients, with baseline metabolic parameters that were monitored at several time-points (baseline and/or 1, 3, 6, 9, 12 months). IDF and World Health Organization definitions were used to define MetS and obesity, respectively. The prevalence of MetS and obesity were 22% and 17%, respectively, at baseline and 32% and 24% after 1 year. ROC analyses suggested that an early weight gain >5% after a period of 1 month was the best predictor for longer-term weight gain ($\geq 15\%$ after 3 months: sensitivity, 67%; specificity, 88%; $\geq 20\%$ after 12 months: sensitivity, 47%; specificity, 89%). The authors therefore suggest that following the prescription of psychotropic drugs, a 5% threshold for weight gain after 1 month should raise concerns about weight-controlling strategies.¹⁴² This would of course mean an early follow-up in these patients.

The prevalence of MetS in schizophrenic patients taking olanzapine monotherapy for at least six months and to determine the most important risk factors associated with the presence of MetS, was studied in 93 long term hospitalized schizophrenic patients (71 men, 22 women). The prevalence of MetS according to IDF criteria was 34.4%. Multivariate analysis showed that a family history of DM (p = 0.002), body mass index >25 kg/m² (p = 0.002), family history of dyslipidaemia (p = 0.008), and elevated serum CRP (p = 0.042) were determinants of MetS. There was a high rate of MetS in patients treated with olanzapine.¹⁴³

The relationship between MetS, severity of psychiatric symptoms, living arrangements, health behaviour and antipsychotic medication was investigated in outpatients with schizophrenia spectrum disorders. A general practitioner and psychiatric nurses performed a comprehensive health examination for all the patients with schizophrenia spectrum disorders treated in a psychosis outpatient clinic. MetS was made according to IDF definition. 276 patients (152 men), the mean age of the group was 44.9 ± 12.6 years. Of the group, 58.7% had MetS. Treatment with clozapine doubled the risk of MetS (OR = 2.04, 95% CI 1.09–3.82, P = 0.03).¹⁴⁴

10. Managing CVD risk in patients with psychiatric disorders

10.1. Drug treatment

There appear to be significant differences in the risks of developing metabolic abnormalities with the different available SGAs (see Table 5). This is likely to be due to differential, off-target effects of these SGAs on receptors for neurotransmitters that include central 5-hydroxytryptamine-2C and histamine-H1 receptors, and peripheral M3-muscarinic receptors.¹⁴⁵ It may be possible to avoid these potentially adverse effects by switching to those with the least metabolic impact. It is also evident that the likelihood of longer-term weight gain and MetS can be determined within a few weeks of starting treatment with SGAs. Screening for weight gain and impaired glucose tolerance would appear to be important, if longer term CVD risk is to be avoided. This also implies that there should be a baseline assessment of CVD risk factors. Adherence to American Psychiatric Association/American Diabetes Association consensus statement recommendations on rates of baseline lipid monitoring is disappointingly low in the absence of systems to encourage or systematise best practice,¹⁴⁶ and despite the high prevalence of CVD risk factors in the population with SMI, there are considerable variations in screening for these risk factors and a need for improvement in some populations and settings.¹⁴⁷

The benefits of treatment with statins in the secondary prevention of CVD are well established,¹⁴⁸ although for primary prevention, even in individuals at high-risk, the benefits are contended with respect to all-cause mortality.¹⁴⁹ Psychiatric complications do not appear to be a prominent feature among the spectrum of reported adverse effects of statins.¹⁵⁰ Statins are however, associated with an increased risk of incident DM and myopathy,¹⁴⁸ although the risk-benefit ratio appears to favour statin use.¹⁴⁸ The value of using statins in low-risk subjects remains debatable.¹⁵¹

Table 5
Impact of specific antipsychotic drugs on weight gain.

Risk of weight gain	Drugs
High	Clozapine, Olanzapine, Quetiapine, Zotepine
Moderate	Amisulpride, Asenapine, Iloperidone, Paliperidone, Quetiapine, Risperidone and Sertindole
Low	Aripiprazole, Lurasidone and Ziprasidone

Overweight, obesity, dyslipidaemia, DM, and MetS are common in patients with SMI, and these co-morbidities increase the risk of mortality. Given the increased risk of CVD in patients with SMI, statin use should at least be considered in the primary prevention of cardiovascular and cerebrovascular events in psychiatric patients, especially in those at high risk.¹⁵² The use of atypical antipsychotics and the presence of SMI are now both included in the QRISK3 algorithm for assessing CVD risk in the United Kingdom.¹⁵³

Peroxisome Proliferator-Activated Receptors (PPARs) are a family of nuclear receptors that are involved in nutrient sensing and whose activation modulate the expression of genes involved in glucose and lipoprotein metabolism and the inflammation pathways.¹⁵⁴ PPAR agonist, for example the fibrate class of drugs, have been used for several years in the treatment of metabolic abnormalities, such as dyslipidaemia, there has been increasing attention on their use for inflammation-related conditions. In the field of psychiatry, it has recently emerged that inflammatory processes are involved in the pathophysiology of several important disorders, such as schizophrenia and mood disorders.¹⁵⁵ Fibrates are sometimes necessary to treat severe hypertriglyceridaemia, which is associated with SGA treatment, if an alternative cannot be found.¹⁵⁶

10.2. Life style interventions

A sedentary lifestyle is an independent predictor of cardiovascular disease.¹⁵⁷ Van Camfort et al. investigated the associations between sitting time (as a proxy for a sedentary lifestyle), physical fitness and metabolic parameters in 219 patients with BD. A higher BMI, poorer physical fitness and higher dose of antipsychotic medication were independent predictors of higher levels of sitting behaviour. The model explained 76.5% of the variability in the sitting time.¹⁵⁸ Interventions that target a sedentary lifestyle are probably necessary in patients with SMI, including BD. Eskilinen et al. have reported that self-reported regular physical activity decreased the risk of MetS significantly.¹⁴⁴

In a meta-analysis of 26 studies that examined the impact of lifestyle interventions on CVD risk factors, Fernandez-San-Martin and colleagues have reported a significant improvement in anthropometric (BMI and waist circumference) and biochemical parameters (fasting blood glucose, and fasting triglycerides and total cholesterol) at 3 months that were maintained at 12 months.¹⁵⁹ Some of the practical difficulties of introducing a combined intervention of diet and physical activity are described by Masa-Font and colleagues¹⁶⁰ in the CAPICOR trial of men with schizophrenia. This suggests that long term compliance is necessary for any significant impact on CVD risk factors. In their systematic review of dietary interventions, Teasdale and colleagues report that dietician-led and early interventions appeared to have the greatest impact on weight control.

¹⁶¹The role and importance of the intestinal microbiota in human health is now being better understood.¹⁶² Recent studies have reported a strong impact of antipsychotics on intestinal microbiota composition,¹⁶³ and this may have an impact on adiposity.¹⁶⁴ Experimental models suggest that treatment with prebiotics may be effective in limiting weight gain following treatment with antipsychotics.¹⁶⁵

11. Conclusions

MetS is a common constellation of cardiovascular risk factors. Its prevalence appears to be higher among some groups of patients with psychiatric disease, such as schizophrenia and BD, and this may, in part, account for the increased morbidity and mortality in these patients. The relationship between SMI and MetS is complex. SMI may cause a predisposition to MetS; features of MetS, such as

obesity, may exacerbate SMI, and there are likely to be common risk factors that contribute to both conditions. Treatment with antipsychotics and anti-depressive drugs may increase the risk of MetS even further. This may be due to off-target effects of these drugs, including effects on appetite, weight gain, and sedentariness. The impact on weight gain appears to occur within weeks, and weight gain during this time may be predictive of much greater weight gain in the longer term. Despite the very high risk of CVD in patients with psychiatric disease, physical screening for MetS and weight gain after commencing treatment with SGA appears to be sub-optimal in most settings. Lifestyle interventions, such as increasing physical activity and dietary change clearly have an important part to play in reducing the risk of MetS in patients with SMI, and need to be implemented at an early stage.

Declarations of interest

Nil.

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